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Bleul, U ; Bylang, T

**Abstract:** A number of drugs have been used to treat asphyxia in new-born calves and the aim of the current study was to investigate the effect of commonly-used stimulant drugs on ventilation, arterial blood gas and acid base variables. A group (n = 18) of new-born (3–15 h old) calves were treated in a randomised sequence with doxapram (40 mg, IV), lobeline (5 mg, IV) or prethcamide (5 mL, consisting of 375 mg crotethamide and 375 mg cropropamide, buccally). Blood and spirometric measurements, using an ultrasonic spirometer, were collected prior to and 1, 5, 15, 30, 60, 90 min after administration of each drug. Doxapram caused a significant increase in the respiratory rate, peak inspiratory and expiratory flow and minute volume (Vmin) during the 90-min post-treatment study period, although maximum values occurred 1 min after treatment. The Vmin increased from  $13.8 \pm 5.0$  L to  $28.5 \pm 12.3$  L. Prethcamide, but not lobeline, also caused significant increases in inspiratory and expiratory volumes. The effects of doxapram on ventilation were accompanied by an increase in arterial partial pressure of oxygen (PaO<sub>2</sub>) ( $77.7 \pm 18.8$  mm Hg to  $93.2 \pm 23.7$  mm Hg), a decrease in arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) ( $42.6 \pm 4.9$  mm Hg to  $33.1 \pm 6.6$  mm Hg), a significant increase in pH and a decrease in bicarbonate concentration and base excess 1 min after treatment. Prethcamide caused a gradual increase in PaO<sub>2</sub> and decrease in PaCO<sub>2</sub> over 90 min, whereas lobeline had no measurable effect on the investigated variables. Of the three treatments, only doxapram had a distinct stimulatory effect on respiration in healthy neonatal calves and may therefore be useful in the treatment of calf asphyxia.

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**Original article**

**Effects of doxapram, prethcamide and lobeline on spirometric, blood gas and acid-base variables in healthy newborn calves**

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## Abstract

A number of drugs have been used to treat asphyxia in newborn calves and the aim of the current study was to investigate the effect of commonly-used stimulant drugs on ventilation, arterial blood gas and acid base variables. A group ( $n=18$ ) of newborn (3 – 15 h-old) calves were treated in a randomised sequence with doxapram (40 mg, IV), lobeline (5 mg, IV) or prethcamide (5 mL, consisting of 375 mg crotethamide and 375 mg cropropamide, buccally). Blood and spirometric measurements, using an ultrasonic spirometer, were collected prior to and 1, 5, 15, 30, 60, 90 min after administration of each drug. Doxapram caused a significant increase in the respiratory rate, peak inspiratory and expiratory flow and minute volume ( $V_{\min}$ ) during the 90-min post treatment study period, although maximum values occurred 1 min after treatment. The  $V_{\min}$  increased from  $13.8 \pm 5.0$  L to  $28.5 \pm 12.3$  L. Prethcamide, but not lobeline, also caused significant increases in inspiratory and expiratory volumes. The effects of doxapram on ventilation were accompanied by an increase in arterial partial pressure of oxygen ( $P_aO_2$ ) ( $77.7 \pm 18.8$  mmHg to  $93.2 \pm 23.7$  mmHg), a decrease in arterial partial pressure of carbon dioxide ( $P_aCO_2$ ) ( $42.6 \pm 4.9$  mmHg to  $33.1 \pm 6.6$  mmHg), a significant increase in pH and a significant decrease in bicarbonate concentration and base excess at 1 min after treatment. Prethcamide caused a gradual increase in  $P_aO_2$  and decrease in  $P_aCO_2$  over 90 min, whereas lobeline had no measurable effect on the investigated variables. Of the three treatments, only doxapram had a distinct stimulatory effect on respiration in healthy neonatal calves and may therefore be useful to treat asphyxia in calves.

**Keywords:** Spirometry; Newborn calves; Blood gas; Doxapram; Lobeline; Prethcamide

## Introduction

The high rate of perinatal calf mortality following dystocia is a significant problem in many countries (Meyer et al., 2001; Berglund et al., 2003; Steinbock et al., 2003) and has many different causes (Lombard et al., 2007; Mee, 2008b; Gulliksen et al., 2009; Gundelach et al., 2009; Bleul, 2011). Critical factors are respiratory and metabolic acidosis, referred to as asphyxia, caused by hypoxia and hypercapnia (Szenci et al., 1988). Severe asphyxia can lead to impaired respiration or even apnoea and this is mainly attributable to depression of the respiratory centre (Daniel et al., 1966; Phillips et al., 2001). This depression can lead to a reduced respiratory drive and calves may fail to develop a normal respiratory pattern and hypoxia and hypercapnia are exacerbated.

In an attempt to break this vicious circle, numerous respiratory stimulants have been used in a variety of species, including human babies (Beretta et al., 1973; Gupta and Moore, 1973; Szenci, 1986; Bleul et al., 2010). The mechanisms of action of the various stimulants vary with the site of action, with some having a general stimulatory effect on the central nervous system, while others stimulate chemoreceptors in the carotid artery or aortic bodies. The site of action may be dose-related (Plumb, 2005). The most commonly used respiratory stimulants in veterinary medicine are doxapram, lobeline and prethcamide (Kochli, 1969; Szenci, 1986; Herfen, 1997; Kersting, 1997; Richter, 2005; Giguere et al., 2008).

Doxapram affects chemoreceptors of the carotid artery and aorta. This is mediated by potassium channels, which belong to the TASK  $K_{2P}$  channels. However, doxapram also has a direct effect on the respiratory centre, but the mechanism of action is unknown (Yost, 2006). It was recently reported that glial cells are involved in the excitatory effects of doxapram on rat

brainstem slices in vitro (Li et al., 2010). In the healthy newborn calf, doxapram induces a distinct increase in respiratory rate (RR) and a decrease in  $P_a\text{CO}_2$  in arterial blood (Bleul et al., 2010). Lobeline acts on nicotinic receptors and its respiratory analeptic effect is mainly mediated by stimulating vegetative ganglia. In the adult horse, lobeline causes an increase in RR and decrease in  $P_a\text{CO}_2$  (Marlin et al., 2000). Prethcamide is composed of a mixture of cropropamide and crotethamide and is believed to increase primarily the tidal volume via stimulation of the respiratory centre, whereas its effect on RR is minimal (Sams et al., 1997). The specific mechanism and site of action of prethcamide is unknown, although the effect of all three respiratory stimulants on ventilation is independent of the partial pressure of  $\text{CO}_2$  (Anderton and Harris, 1963; Nishino et al., 1982; van Lunteren et al., 1984).

Although doxapram, lobeline and prethcamide are approved for use in neonatal calves in many countries, there is only limited information on their effect on venous and arterial blood gas variables (Szenci, 1986; Herfen, 1997; Bleul et al., 2010). The aim of the current study was to investigate if doxapram, lobeline and prethcamide would cause measurable changes in spirometric (using ultrasonic spirometry), pulmonary gas exchange (evaluated using blood gas analysis) and acid-base variables in healthy newborn calves. Any drug improving the indices of spontaneous breathing may therefore be to treat asphyxia in neonatal calves.

## **Material and methods**

### *Animals*

Eighteen calves, consisting of 11 Swiss Braunvieh, 6 Holstein Frisian and 1 Swiss Braunvieh x Simmental calves, were used for the study. There were 12 heifer calves and six bull calves with a bodyweight (BW) of  $45 \pm 5$  kg (mean  $\pm$  SD) and were born after a gestation of 288

± 6 days. The calves underwent a clinical examination and venous blood gas analysis using a blood gas analyser (Rapidlab 248, Siemens). Results of clinical examination were normal and there were no signs of circulatory or pulmonary abnormalities. All the calves had a venous blood pH >7.2. At the beginning of the experiment the calves were between 3 - 15 h old.

#### *Catheters*

The placement sites for catheters were shaved and disinfected with alcohol. For collection of arterial blood, an 18 G indwelling catheter (Neolus) was placed in the medial intermediate branch of the caudal auricular artery and fastened with cyanoacrylate glue in 12 calves. In the remaining six calves, access to this artery was not possible and a 22 G catheter (Neolus) was placed in a femoral artery after local administration of 2 mL lidocaine (Lidocain-Hyaluronidase 2%, Streuli) and fixed in place with a suture. For the administration of drugs, a 14 G indwelling catheter was placed in a jugular vein after local administration of 2 mL lidocaine (Lidocain-Hyaluronidase 2%, Streuli) and sutured in place.

#### *Administration of respiratory stimulants*

The study was a randomised three-way cross-over design, with each treatment administered at the end of a 15 min resting period. Calves were randomly assigned to receive either doxapram (40 mg, IV; Dopram-V, Albrecht), lobeline (5 mg, IV; Zoolobelin, Arovet) or prethcamide (5 mL, buccally, consisting of 375 mg crotethamide and 375 mg cropropamide; Respirot, Novartis). The drug doses were based on the manufacturer's recommendations guidelines or from published studies (Beretta et al., 1973; Bureau et al., 1999a; Herfen and Bostedt, 1999; Bleul et al., 2005). Measurements were carried out for 90 min after administration, which was followed by a wash-out period of 2 h before the next drug was given. Another 2 h

wash-out period followed the 90 min measurement period, and then the third drug was given. The study design ensured that all three respiratory stimulants were administered in a random order to avoid potential confounding effects of the sequence of administration.

### *Blood sampling*

Arterial blood samples for blood gas analysis were collected before administration (baseline) and arterial and venous blood samples 1, 5, 15, 30, 60 and 90 min after administration of the stimulant. Blood gas monovettes coated with calcium-balanced heparin to generate a concentration of 50 IU heparin/mL blood (Sarstedt) were used for blood gas analysis.  $P_aO_2$  and  $P_aCO_2$  and oxygen saturation ( $sO_2$ ) were measured either immediately after blood collection or within 30 min of collection, during which time the blood samples were stored on ice. The blood pH, bicarbonate concentration ( $HCO_3^-$ ) and base excess (BE) were also measured using the blood gas analyser (Rapidlab 248, Siemens). This instrument uses three different sensors for measuring  $P_aO_2$ ,  $P_aCO_2$  and pH, which are corrected for body temperature of the calf. The remainder parameters were calculated by the blood gas analyser.

### *Spirometry*

Heart and respiratory rates and body temperature were measured immediately before each blood collection, after which spirometric measurements were carried out using an ultrasonographic spirometer (Exhalyzer D, Eco Medics). The principle of ultrasonographic spirometry is based on the measurement of two transit times of ultrasonographic waves across a tubular sensor. Measurements were not affected by the composition, temperature and humidity of the air. Ultrasonic pulses were emitted from two transducers in opposite positions. The tubular spirette (respiratory tube) through which the calf breathes was positioned at an acute angle to the

ultrasonic pulses. Movement of air in the spirette results in changes of the transit time (time of flight) of the sound waves, which was used to calculate the velocity of air flow (Buess et al., 1986). The spirometer was calibrated daily according to the manufacturer. An anaesthetic mask, equipped with a rubber collar, with an approximated equipment dead space of 1500 mL, as determined by water displacement, was used for the measurements (Fig. 1). The anterior opening of the mask was adapted to the size of the spirette such that the entire airflow passed through it.

Once the standing calf was accustomed to the mask, which usually took 30 s to 1 min, measurements were carried out for a period of 1 min before the respiratory stimulant was administered. All other measurements were made after blood sampling 1, 5, 15, 30, 60 and 90 min after administration of the stimulant. The spirometric data were transferred to a computer and analysed using a software program (Spiroware 3.0, Eco Medics). Based on the velocity of air flow, the volumes of inhaled and exhaled air were calculated, from which the following variables were derived. The volume measured during each inspiration and expiration was expressed for each breath as  $V_{in}$  (L) and  $V_{exp}$  (L). The minute volume ( $V_{min}$ , L) was calculated using the formula  $(V_{in} + V_{exp}) \times 0.5 \times RR$ . Finally, the peak inspiratory flow (PIF, L/s) and peak expiratory flow (PEF, L/s) and the ratio of duration of expiration and duration of inspiration ( $T_{exp}/T_{in}$ ) were calculated.

#### *Statistical analysis*

The data were checked for normal distribution using the Shapiro-Wilk test and statistical analyses were performed using Stat View 5.0 (SAS Institute). All parameters were normally distributed, so results were given as mean  $\pm$  standard deviation ( $\bar{x} \pm SD$ ). To verify if the results were influenced by the sequence of administered stimulant, one-way ANOVA was used to



compare baseline values of the three treatment periods. Differences in the course over time of various variables within a treatment group and between respiratory stimulants were analysed using ANOVA for repeated measures. If ANOVA revealed no significant differences in the course over time of the variables, Fisher's PLSD post-hoc test was used for comparison among stimulants at individual measuring times. In case ANOVA revealed statistical differences over time within a treatment group, paired *t* test was used for comparison among values at different time points. *P*-value  $\leq 0.05$  was considered significant.

This study was approved (92/2008) by the Committee for the Permission of Animal Experimentation of the Canton of Zurich.

## Results

Clinical signs indicative of adverse side effects of the respiratory stimulants were not observed in any of the calves during the study period. The anaesthetic mask was well tolerated and no disturbances of the spirometric measurements due to movements of the calves were observed. There were no significant differences in baseline values between treatment groups for any measured variables. The rectal temperature ranged from 38.3 - 38.8 °C and the heart rate from 109 - 129 beats/min; there were no significant changes over time in the latter variable. Within 1 min of doxapram administration, the RR increased from  $69 \pm 23$  breaths/min to  $105 \pm 33$  breaths/min ( $P < 0.001$ ; Fig. 2a). Lobeline and prethcamide had no significant effect on RR.

### *Spirometry*

Lobeline and prethcamide had no effect on PIF and PEF, whereas doxapram led to an increase in both PIF and PEF ( $P < 0.001$ ). The highest PIF value of  $1.59 \pm 0.69$  L/s occurred 1

min after doxapram administration, and the measurements remained significantly higher than the baseline value of  $0.79 \pm 0.21$  L/s for 60 min (Fig. 2b). Likewise, the PEF increased from the baseline value of  $0.78 \pm 0.24$  L/s to a maximum of  $1.44 \pm 0.58$  L/s 1 min after doxapram treatment and remained significantly increased for the entire study period of 90 min.

The three treatments did not differ with respect to the time courses of  $V_{in}$  and  $V_{exp}$ . One min after treatment  $V_{in}$  was different between the doxapram and the lobeline group ( $P < 0.05$ ). After treatment with doxapram,  $V_{in}$  and  $V_{exp}$  increased within 1 min from  $0.28 \pm 0.08$  L -  $0.33 \pm 0.06$  L and from  $0.21 \pm 0.07$  L -  $0.27 \pm 0.05$  L, respectively ( $V_{in} P \leq 0.05$ ;  $V_{exp} P < 0.001$ ). After treatment with prethcamide,  $V_{in}$  and  $V_{exp}$  increased within 1 min from  $0.26 \pm 0.08$  L -  $0.31 \pm 0.10$  L and from  $0.25 \pm 0.10$  L -  $0.27 \pm 0.10$  L, respectively ( $V_{in} P \leq 0.05$ ;  $V_{exp} P \leq 0.05$ ). Lobeline did not affect  $V_{in}$  and  $V_{exp}$ .

Doxapram differed significantly from prethcamide and lobeline with respect to the time course of  $V_{min}$  (Fig. 2c;  $P < 0.001$ ). After treatment with doxapram,  $V_{min}$  increased within 1 min from  $13.83 \pm 5.00$  L to a maximum value of  $28.45 \pm 12.31$  L. The measurements decreased gradually, but remained significantly higher than the baseline value until the last measurement 90 min after treatment. Prethcamide and lobeline did not affect  $V_{min}$ .

The ratio  $T_{exp}/T_{insp}$  was not affected by any of the treatments, and the course of  $T_{exp}/T_{insp}$  over time did not differ among treatments. The mean baseline value before treatment was  $1 \pm 0.24$ . Irrespective of the respiratory stimulant, the lowest value was  $0.97 \pm 0.19$  measured 5 min after treatment and the highest  $1.01 \pm 0.30$  after 30 min.

### *Blood gas analysis*

Over the 90 min recording period, there were significant differences among the three treatments with respect to  $P_aO_2$  (Fig. 3a). Doxapram led to a significant increase in  $P_aO_2$  from  $77.7 \pm 18.9$  mmHg to a maximum value of  $93.2 \pm 23.7$  mmHg at 1 min. Prethcamide caused a significant increase in  $P_aO_2$  at 90 min compared with values before and 1, 5, 15 and 30 min after treatment (all  $P < 0.01$ ). Lobeline did not affect  $P_aO_2$ .

There were significant differences among the three treatments with respect to  $P_aCO_2$  ( $P < 0.0001$ ). Doxapram caused a significant decrease in  $P_aCO_2$  from a baseline value of  $42.6 \pm 4.9$  mmHg to  $33.1 \pm 6.6$  mmHg at 1 min, and the measurements remained decreased throughout the study period (Fig. 3b). Prethcamide caused a significant gradual decrease in  $P_aCO_2$  from the baseline value of  $42.0 \pm 4.9$  mmHg to a minimum of  $38.5 \pm 6.4$  mmHg at 30 min ( $P \leq 0.05$ ). Lobeline did not affect  $P_aCO_2$ .

The  $sO_2$  profiles of arterial blood did not differ among treatments. Doxapram caused a transient increase in  $sO_2$  from a baseline value of  $91 \pm 10\%$  -  $95 \pm 7\%$  at 1 min ( $P < 0.01$ ).

### *Acid base variables*

Doxapram, but not prethcamide and lobeline, significantly affected arterial pH, bicarbonate concentration and BE. Doxapram caused a significant increase in arterial pH from a baseline value of  $7.45 \pm 0.06$  -  $7.51 \pm 0.05$  at 1 min (Fig. 3c;  $P < 0.0001$ ). Bicarbonate concentration decreased after doxapram from a baseline value of  $28.2 \pm 4.1$  mmol/L and reached a minimum of  $25.2 \pm 4.1$  mmol/L at 5 min ( $P \leq 0.05$ ). Base excess in arterial blood decreased

from a baseline value of  $4.3 \pm 2.9$  mmol/L and reached a minimum of  $2.4 \pm 4.5$  mmol/L at 5 min ( $P \leq 0.05$ ).

In venous blood, only pH was affected by treatment. During the entire post-treatment study period, the venous pH was higher after treatment with doxapram than after treatment with prethcamide and lobeline ( $P < 0.001$ ).

## Discussion

Disturbances in respiratory adaption to extra-uterine life are a major cause of perinatal mortality in calves (Eigenmann, 1981; Szenci, 2003). A variety of physical and pharmacological measures are commonly used in an attempt to correct these disturbances immediately after calving (Winnie, 1973; Szenci, 1986; Uystepuyst et al., 2002). Physical measures, including the use of a suction pump to remove fluid from the pharynx and nose, pouring cold water into the ears and over the head and warming the calf using an infrared radiant heater, only had minor effects on arterial blood gas and respiratory variables in newborn Belgian white blue calves that did not have asphyxia. However, pharyngeal and nasal suctioning reduced the  $p\text{CO}_2$  and warming the calves increased arterial  $s\text{O}_2$ , and both measures changed the breathing pattern to deeper and slower breathing compared with non-treated controls (Uystepuyst et al., 2002). In the current study, doxapram caused distinct changes in respiratory variables in healthy 3 - 15 h old neonatal calves, leading to a significant increase in mean minute volume by 106% within 1 min after treatment. Mean minute volume before treatment was similar to published values (Varga et al., 1999). In lambs, doxapram (2.5 mg/kg BW) increased the  $V_{\text{min}}$  by 54% (Bairam et al., 1990). Similarly, doxapram (loading dose of 0.5 mg/kg, followed by a 20-min infusion at 0.03

mg/kg/min and then 0.08 mg/kg/min) caused increases in RR and  $V_{\min}$  by more than 100% in anaesthetised 1- 3 day-old foals with induced hypercapnia, (Giguere et al., 2007).

The distinct rise in the minute volume in our study was more likely induced by an increase in peak inspiratory and expiratory flows than by an increase in RR, because RR rose only by 52%, whereas PIF and PEF increased by 102% and 86%. This was in agreement with a previous study involving 2 - 6 h old calves without asphyxia in which doxapram caused a similar increase in RR from a mean of 56 - 106 breath/min (Bleul et al., 2010). The results of the current study therefore demonstrated that doxapram (40 mg IV) had a noticeable effect on ventilation, reflected by an increase in the amount of air that is inhaled and exhaled by the calf, which in turn increased pulmonary gas exchange (a transient increase in  $P_aO_2$  and a distinct decrease in  $P_aCO_2$  within 1 min of doxapram administration).

These improvements in pulmonary gas exchange and the rapid (within 30 s) increase in pH ( $7.37 \pm 0.04$  -  $7.53 \pm 0.07$ ) have been reported previously (Bleul et al., 2010). The marked increase in mean minute volume after the doxapram treatment could have induced hyperventilatory hypocapnia ( $P_aCO_2 < 35$  mmHg), which may have resulted in a rise in pH to the alkalotic range. A low  $P_aCO_2$  causes a shift in the carbonic-acid-bicarbonate equilibrium toward  $CO_2$  and  $H_2O$  production (Meyfeldt, 2004), which is associated with decreasing bicarbonate concentration and decreasing BE, consistent with the current study, for at least 15 min. Hypocapnia has been associated with cerebral vasoconstriction, which in turn can lead to cerebral hypoxia (Funderburk et al., 1968). However, the calves in the current study did not present any clinical signs of depression or neurological disorders. Furthermore, asphyxic neonatal calves have a  $P_aCO_2$  that is approximately twice as high as the pressures measured in calves without asphyxia

in the current study, which would make a decrease in the  $P_a\text{CO}_2$  into the hypocapnic range in response to doxapram treatment unlikely. Acidotic neonatal calves delivered by caesarean section and treated with doxapram immediately after birth had a decrease in  $P_v\text{CO}_2$  (Szenci, 1986) that was lower than in untreated controls (Herfen, 1997). In both of these studies, hypocapnia did not occur, but the  $P_v\text{CO}_2$  remained above 45 mmHg in the hypercapnic range. However, these studies used venous blood, where the  $P_v\text{CO}_2$  is determined primarily by the bicarbonate in the periphery.

Published reports on the efficacy of prethcamide for the establishment of a normal breathing pattern in newborn calves are equivocal. In one study, prethcamide had no effect in neonatal calves, with or without asphyxia, as determined by venous blood gas analysis and clinical examination (Herfen, 1997). In another study in non-acidotic calves delivered by caesarean section, prethcamide significantly reduced pH and 10-60 min post-partum, compared to untreated controls (Szenci, 1986). In contrast, prethcamide induced significant increases in  $P_a\text{O}_2$  and decreases in  $P_a\text{CO}_2$  changes in arterial blood that indicated improvement in ventilation in the current study, possibly due to larger tidal volumes ( $V_{\text{in}}$  and  $V_{\text{exp}}$ ), as has been reported in humans (Sams et al., 1997). However, prethcamide had no effect on minute volume and we were unable to explain the relationship between the increasing tidal volumes immediately after prethcamide administration and the changes in  $P_a\text{CO}_2$  seen 30 min and in  $P_a\text{O}_2$  90 min post treatment.

Pharmacokinetic studies have shown that the maximum concentration of prethcamide in blood is reached 3 min after oral administration and has decreased by 66% by 60 min (Anonymous, 1998). In the current study, the stimulatory effect of oral prethcamide on respiration was generally minimal and improvements in blood gas variables were greatly delayed, so this drug may not be useful to treat acute asphyxia. However, it is possible that the positive

effect of prethcamide is more pronounced in animals with a very high  $P_a\text{CO}_2$ , although the effect of prethcamide is believed to be independent of  $P_a\text{CO}_2$ , except for specific limits (Anderton and Harris, 1963).

Surprisingly, both spirometric measurements and blood gas analysis failed to show a positive effect of IV of lobeline on ventilation. There have been several studies in human and veterinary medicine that showed an increase in RR and tidal volume after the administration of lobeline (Winnie, 1973; Herholz et al., 2001). In Holstein and Belgian blue calves with a mean BW of  $143 \pm 20$  kg, an increase in both variables occurred, which in turn was associated with a rise in  $V_{\min}$  (Bureau et al., 1999a). Possible reasons why lobeline failed to have an effect were the dose used and the age of the calves. We used the 5 mL dose (5 mg) recommended by the manufacturer for calves with a mean BW of 45 kg ( $\sim 0.11$  mg/kg BW), while another study used four different doses of lobeline ranging from 0.05 - 0.35 mg/kg BW IV (Bureau et al., 1999a). When lobeline was used at a dose similar to the one in the current study (0.15 mg/kg BW), there were significant increases in RR, tidal volume and minute volume, compared with baseline values and values elicited by lower doses. It was therefore more likely that the lack of effect of lobeline was age rather than dose related, particularly when considering lobeline was less effective in 10 day-old foals (Marlin et al., 1997) and calves less than 2 weeks old (Bureau et al., 1999b), compared to mature animals.

Any age-related difference may be due to a lower responsiveness of the neonatal respiratory centre to stimulant drugs, since the sensitivity to oxygen rises during the postnatal period in rats (Eden and Hanson, 1987). A critical factor in the current study was the very short duration of action of lobeline. In previous studies, RR reached a maximum 5 s after

administration of the drug, tidal and minute volumes were maximal after 30 s and had declined considerably by 1 min (Bureau et al., 1999a). It is therefore possible that the maximum values for respiratory rate and tidal and minute volumes were missed in the current study since the first measurement was recorded 1 min after treatment, although we would have expected that lobeline would have led to some detectable effect in the blood after 1 min. Newborn non-acidotic calves showed a decrease in venous pH, BE and  $\text{HCO}_3^-$  10 min after birth (Szenci, 1986). Our results indicated that lobeline at the recommended dose does not significantly stimulate ventilation and does not improve pulmonary gas exchange in neonatal calves up to 24 h old. Further spirometric studies are needed to determine whether higher doses might have a beneficial effect in newborn calves.

## Conclusions

Only doxapram had a distinct stimulatory effect on ventilation in healthy newborn calves, while prethcamide and lobeline did not. Doxapram caused noticeable changes in blood gas and acid base variables, which included a decrease in  $P_a\text{CO}_2$  and increase in  $P_a\text{O}_2$ . These specific effects of doxapram should theoretically be of great benefit in the treatment of neonatal asphyxia because they shorten the postnatal hypoxic phase and duration of respiratory acidosis. Whether these effects do in fact occur when asphyxic calves are treated immediately after birth need to be investigated in future studies.

## Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.



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## Figure legends

Fig. 1. Calf with spirometry equipment held in place by operator during the measurements. (A) mask; (B) spirette; (\*) position of ultrasound transducers.

Fig. 2. (a) Respiratory rate (RR), (b) maximum inspiratory flow (PIF) and (c) minute volume ( $V_{\min}$ ) in 18 calves before and after administration of doxapram (◆), prethcamide (■) and lobeline (▲). (↑) indicates times of treatment and (\*) indicates time points with values significant different to baseline after doxapram treatment.

Fig. 3.  $P_aO_2$  (a),  $P_aCO_2$  (b) and arterial pH (c) in 18 calves before and after the administration of doxapram (◆), prethcamide (■) and lobeline (▲). (↑) indicates times of treatment, (\*) indicates time points with values significant different to baseline after doxapram treatment and (+) indicates time points with values significant different to baseline after prethcamide treatment.

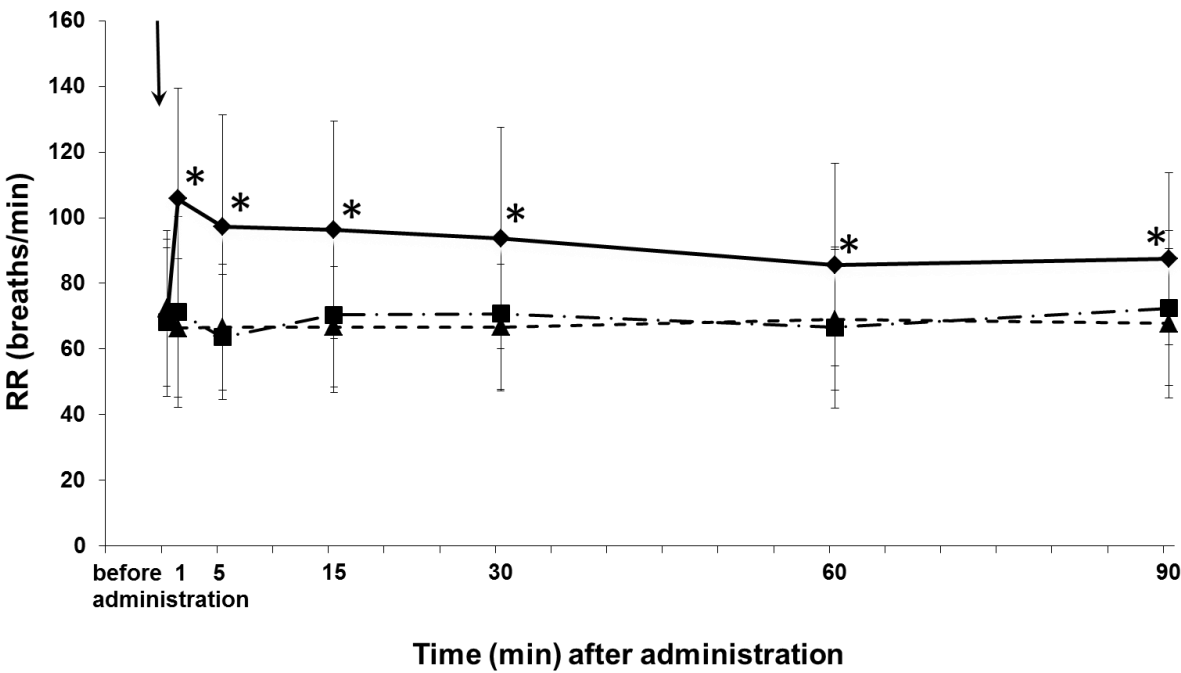


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534 Figure 2a



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Figure 2b

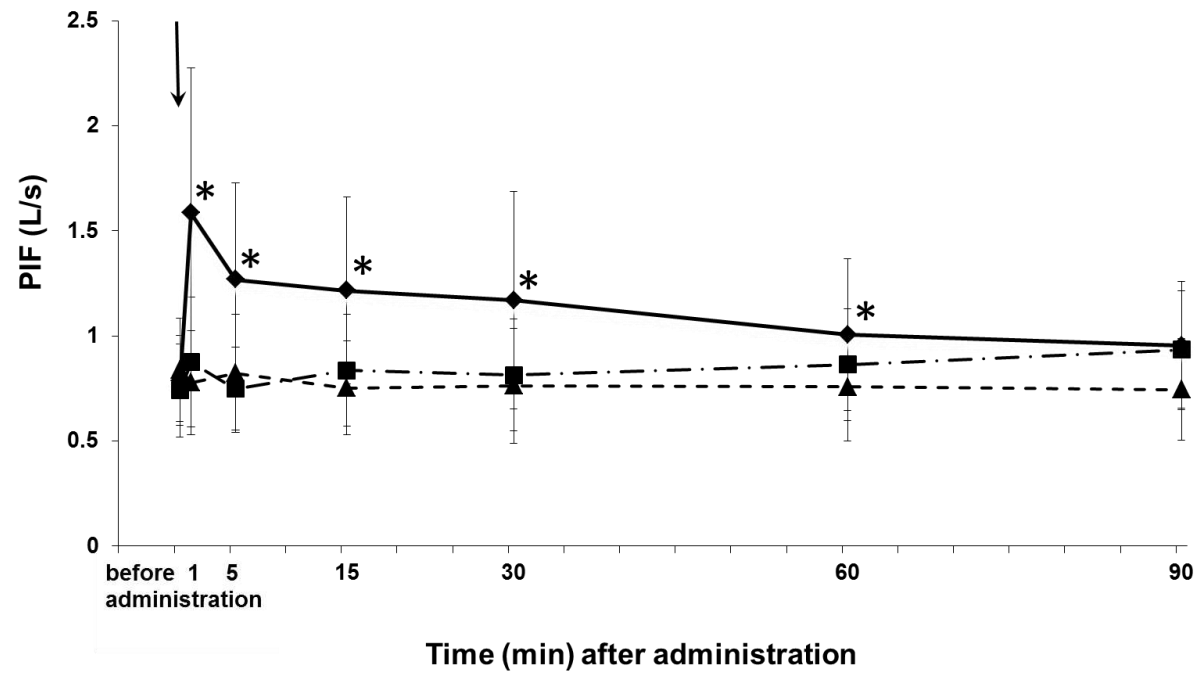




Figure 2c

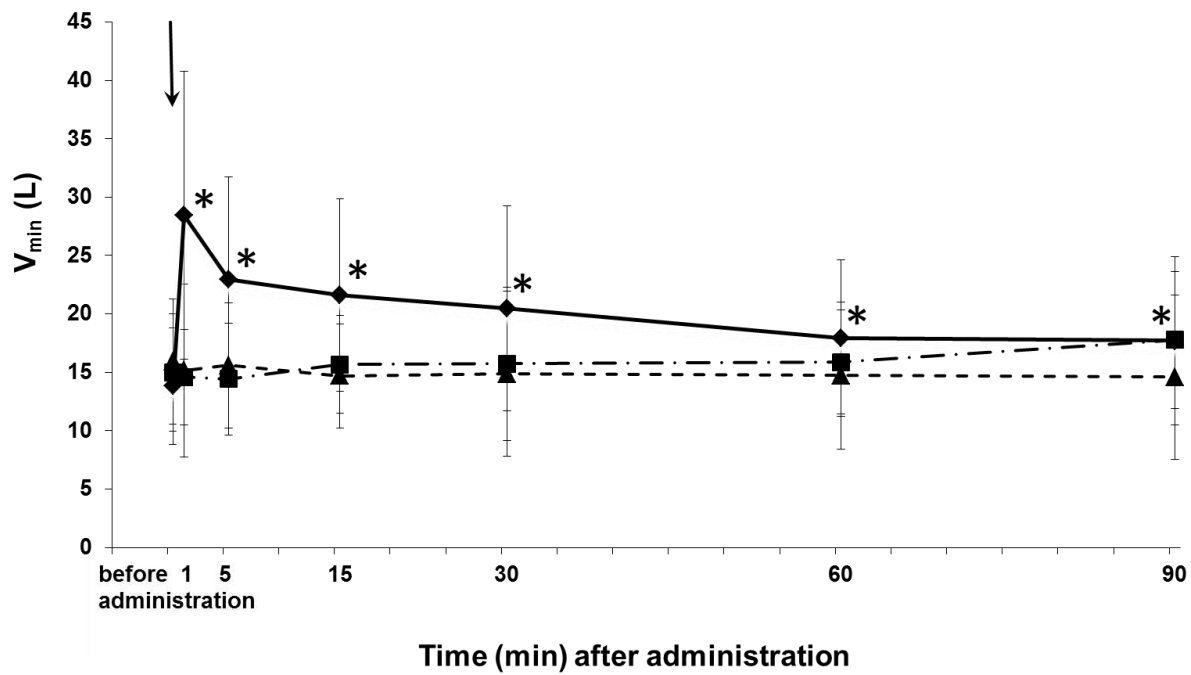


Figure 3a

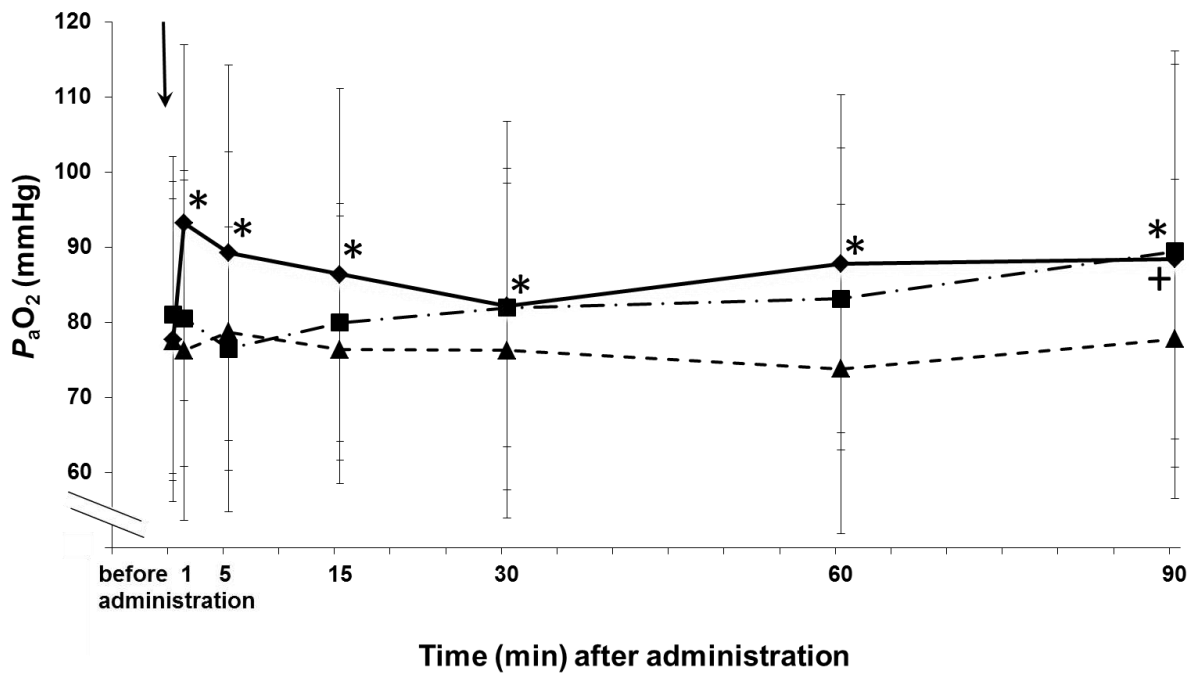


Figure 3b

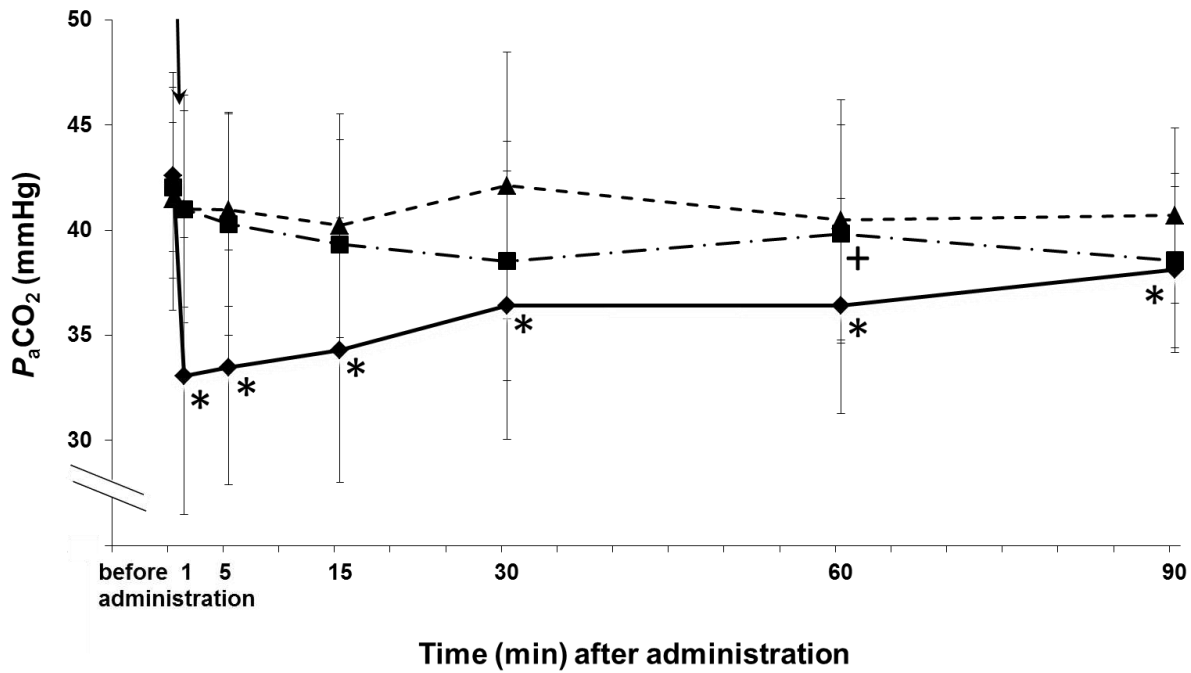


Figure 3c

